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Atty. Dkt. No. 047711-0293

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Rajiv SHAH, et al.

Title: METHOD FOR FORMULATING A GLUCOSE OXIDASE ENZYME WITH A DESIRED PROPERTY OR PROPERTIES AND GLUCOSE OXIDASE ENZYME WITH THE DESIRED PROPERTY

CERTIFICATE OF EXPRESS MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service's "Express Mail Post Office To Addressee" service under 37 C.F.R. § 1.10 on the date indicated below and is addressed to: Mail Stop Appeal Brief - Patents Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

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Kumar Maheshwari
(Printed Name)

(Signature)

Appl. No.: 10/035,918

Filing Date: 12/28/2001

Examiner: Yong D. Pak

Art Unit: 1652

Confirmation Number: 2208

REPLACEMENT SECTION FOR APPEAL BRIEF UNDER 37 C.F.R 41.37

Mail Stop Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

This communication is responsive to the Notification of Non-Compliant Appeal Brief dated May 10, 2007, concerning the above-referenced patent application.

Please amend the Appeal Brief filed on April 02, 2007 as follows:

Amendment to the Appeal Brief:

In accordance with 37 C.F.R. 1205.03, please replace Sections II and V of the Appeal Brief with the following new Sections II and V:

II. RELATED APPEALS AND INTERFERENCES

Applicant is not aware of any related appeals, interferences or legal proceedings that would have a bearing on the Board's decision in the present Appeal. However, Applicant filed a Notice of Appeal from a previous Final Office Action dated July 12, 2005, and filed a corresponding Appeal Brief on December 7, 2005. There was no decision in that Appeal. Instead, following those filings, the Examiner reopened prosecution and issued a new Office Action in which certain rejections raised in the July 12, 2005, Final Office Action were withdrawn and certain new grounds of rejections were raised.

The present patent application claims the priority filing date of U.S. Provisional Application No. 60/335,585 (now expired), for which no substantive examination on the merits was conducted by the U.S. Patent and Trademark Office.

A Continuation Application (Serial No. 10/715,143) is currently pending. A Notice Of Appeal was filed in the Continuation Application on April 16, 2007. No briefs have been filed and no decision has been rendered in that Appeal.

V. SUMMARY OF CLAIMED SUBJECT MATTER

Embodiments of the present invention relate, generally, to a method employing directed evolution techniques for formulating a glucose oxidase enzyme having peroxide-resistant characteristics for use, by way of example, in a sensing device.

An example implantable sensing system contains a sensing device that is inserted into a vein, an artery, or any other part of a human body where it could sense a desired parameter of the implant environment. An enzyme may be placed inside of the sensing device and employed for sensing. If the device is a glucose-sensing device, then a combination of glucose oxidase (GOx)

and human serum albumin (HSA) may be utilized to form a sensor protein. During operation in a sensing device, glucose oxidase reacts with oxygen and oxidizes. The oxidation of glucose oxidase results in the formation of a hydroperoxy adduct, which transforms into hydrogen peroxide.

An obstacle to creating sensors that are long-lived and stable over time has been that glucose oxidase, when immobilized (e.g., for use in a sensor), undergoes oxidative inactivation by the aforementioned hydrogen peroxide over time. Since the lifetime of glucose sensors primarily depends on the lifetime of glucose oxidase, the effects of the peroxide on the glucose oxidase can severely limit the lifetimes of glucose sensors.

Prior processes for addressing the peroxide degradation of glucose oxidase have involved the use of additives or neutralizing agents for deactivating, removing or neutralizing peroxide. (Examples of such prior art are discussed below with respect to the Valdes et al. reference, the Stemmer patent, the Hatzinikolaou et al. article, the Wagner et al. patent, and the Aldrich Catalog page relating to Leuco-crystal violet) Embodiments of the present invention relate to a drastic change in direction of the state of the art by employing directed evolution techniques to formulate a glucose oxidase gene having desired peroxide resistant properties.

Evolution under non-stress circumstances takes years. Accordingly, evolution may be manipulated in embodiments of the invention for specific enzymatic functions. In embodiments of the invention, a technique known as directed evolution is employed to evolve glucose oxidase, to formulate a glucose oxidase that possesses improved resistance to peroxide. A glucose oxidase formulated pursuant to embodiments of the present invention may improve the longevity of a biosensor in which it is employed.

According to the claims under appeal, a method comprises creating a library of mutated glucose oxidase genes. Mutations of glucose oxidase genes may be obtained by performing polymerase chain reaction techniques, error-prone polymerase chain reaction techniques or gene shuffling techniques. Each of the library of mutants is inserted into a separate expression vector.

Each expression vector is inserted into a host organism where a colony can grow, thereby replicating the mutated genes.

The library of colonies is then screened for desirable peroxide resistant properties. The colonies are screened by determining whether the colonies contain active glucose oxidase and determining whether the colonies have desired peroxide resistant properties. Determining whether the colonies have desired peroxide resistant properties involves incubating the colonies in peroxide and determining whether the colonies have active glucose oxidase after incubating, including measuring a concentration of the glucose oxidase.

In one embodiment, after the screening procedure, the glucose oxidase from one or more of the screened colonies may be mutated into a second generation library of mutants. The process may then proceed again with the second generation mutations. In other embodiments, this same process may be repeated many times on subsequent generations of mutated genes until a gene is formulated with suitable properties. In one embodiment the process is repeated from two to six times. In this manner, the mutations may be refined further to provide the desired peroxide resistant properties.

Those colonies that still contain active glucose oxidase after one or more mutation and incubation procedures may possess desirable peroxide resistant qualities. Glucose oxidase from those colonies still containing active glucose oxidase may be tested for functionality, for example, by immobilizing the glucose oxidase in a sensor. In other embodiments of the invention, following at least a portion of the screening procedure, the environments of the colonies may be altered another time if desired, for example, by adding more peroxide.

The method recited in the pending claims of the present application can provide significant advantages over the prior art of record. The ability to form a stable enzyme which is peroxide resistant and which may be employed in an altered environment (oxygen free environment), such as a biosensor, can provide significant advantages in extending the life of biosensors. When used in an implanted medical device (such as an implanted blood glucose

sensor), peroxide resistance and, thus, a capability for extending the life of the enzyme can provide considerable patient comfort and safety advances, for example, by reducing the frequency of surgical sensor replacements. Moreover, the ability to form enzymes with peroxide resistant properties suitable for biosensor applications in a relatively inexpensive, non-complicated and reliable process can provide significant advantages with respect to the ability to manufacture readily available supplies of the enzyme and, thus, increasing the availability of longer-life biosensors to more patients.

By a method in accordance with embodiments of the present invention, a glucose oxidase enzyme may be formulated to exhibit desired peroxide resistant properties. As such, further additives or other mechanisms for deactivating, removing or neutralizing peroxide may not be required. Thus, the disclosed method involves a distinct departure from the conventional direction of those skilled in the art.

Claim 1 is the sole independent claim under consideration in the present Appeal. An example of a mapping of claim 1 to the specification is shown in the following chart.

Claim 1	Specification
A method for formulating an enzyme comprising:	Title; pg. 1, ll. 21-24; pg. 4, ll. 10-22; pg. 7, ll. 11-12.
obtaining a library of glucose oxidase genes;	Pg. 5, ll. 14-16; pg. 8, ll. 6-13; Fig. 2, ref. 12; pg. 14, ll. 1-8.
creating a library of mutated glucose oxidase genes;	Pg. 5, ll. 15-16; pg. 8, l. 14 to pg. 9, l. 9; Fig. 5; pg. 14, ll. 9-14; Fig. 2, ref. 14.
introducing each mutated glucose oxidase gene of the library into separate expression vectors;	Pg. 5, l. 16; pg. 9, ll. 10-16; Fig. 2, ref. 16.

inserting the expression vectors into non-human host organisms;	Pg. 5, l. 17; pg. 9, ll. 17-22; Fig. 2, ref. 16.
growing colonies of the host organisms; and	Pg. 5, l. 17-18; pg 10, ll. 1-9; Fig. 2, ref. 18.
screening the colonies for predefined, desired properties by determining whether the colonies contain active glucose oxidase and determining whether the colonies have predefined, desired peroxide resistant properties,	Pg. 5, ll. 18-21; pg. 10, l. 10 to pg. 13, l. 15; pg. 14, ll. 15-20; Fig. 2, ref. 20.
wherein determining whether the colonies have predefined, desired peroxide resistant properties comprises: incubating the colonies in peroxide; and determining whether the colonies have active glucose oxidase after incubating the colonies in peroxide,	Pg. 11, ll. 15-22; pg. 12, ll. 5-7
wherein determining whether the colonies contain active glucose oxidase comprises: detecting a concentration of active glucose oxidase.	Pg. 11, l. 23 to pg. 12, l. 5

Remarks for Evidence Appendix

Exhibit 1 and 2 are part of the Evidence Appendix. Therefore the sheet on page 8 of this reply labeled "Evidence Appendix" should be placed between the last page of the Claims Appendix and the page labeled Exhibit 1.

EVIDENCE APPENDIX

RELATED PROCEEDINGS

None.

REMARKS

Applicant respectfully requests reconsideration of the present application in view of the foregoing amendments.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check or credit card payment form being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

Date June 6, 2007

By _____

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